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Pneumococcal disease prevention among adults: Strategies for the use of pneumococcal vaccines

Tamara Pilishvili[a,*], Nancy M. Bennett[b]

[a] National Center for Immunizations and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States
[b] Department of Medicine and Center for Community Health, University of Rochester School of Medicine and Dentistry, Rochester, NY, United States

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ABSTRACT

Use of the pneumococcal conjugate vaccines among children in the US since 2000 has dramatically reduced pneumococcal disease burden among adults. Significant vaccine-preventable morbidity and mortality from pneumococcal infections still remains, especially among older adults. The US Advisory Committee on Immunization Practices (ACIP) has recently recommended the routine use of both pneumococcal conjugate (PCV13) and polysaccharide vaccines (PPSV23) for adults ≥65 years. These recommendations were based on the remaining burden of illness among adults and the importance of non-bacteremic pneumonia prevention in light of new evidence confirming the efficacy of PCV13 to prevent pneumococcal pneumonia among older adults. This paper reviews the evidence that led the ACIP to make recommendations for PCV13 and PPSV23 use among adults, and highlights potential gaps to be addressed by future studies to inform adult vaccination policy. The changing epidemiology of invasive pneumococcal disease and pneumonia should be closely monitored to evaluate the effectiveness and continued utility of the current vaccination strategy, and to identify future directions for pneumococcal disease prevention among older adults.

1. Background

Streptococcus pneumoniae is a leading cause of disease and death among older adults in the United States. Pneumococcus causes invasive disease – bacteremia and meningitis – as well as pneumonia. Use of polysaccharide vaccine since the late 1970s should have resulted in the decline of invasive pneumococcal disease (IPD) among older adults but uptake has been slow, and the declines at a population level have not been documented [1–3]. Conversely, use of the conjugate vaccines (7-valent conjugate vaccine (PCV7) and 13-valent conjugate vaccine, (PCV13)) in children since 2000 has dramatically reduced vaccine-type invasive infections in older adults as a result of indirect, "herd" effects [4,5]. Reductions in community-acquired pneumonia (CAP) among adults have also been documented since PCV7 introduction among children [6]. Despite these dramatic indirect benefits of PCV7 and PCV13 use in pediatric populations, significant morbidity and mortality still result from pneumococcal infection in older adults. In 2013, approximately 20–25% of IPD [7] cases and approximately 10% of all CAP [8] cases among adults ≥65 years old were caused by PCV13 serotypes and, therefore, many of these might have been prevented through direct use of PCV13 among adults. This paper will review the evidence that led the Advisory Committee on Immunization Practices (ACIP) to recommend PCV13, and continued use of PPSV23 for adults, and highlight potential gaps to be addressed by future studies to inform adult vaccination policy.

2. Pneumococcal vaccines

2.1. Pneumococcal polysaccharide vaccine—PPSV23

The currently available pneumococcal polysaccharide vaccine, manufactured by Merck, Inc. (Pneumovax® 23), includes 23 purified capsular polysaccharide antigens of *S. pneumoniae* (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). This vaccine was licensed in the United States in 1983 and replaced an earlier 14-valent formulation that was licensed in 1977.

The first PPSV licensed in the US was PPSV14. Capsular polysaccharides included in the current polysaccharide vaccine, PPSV23, induce antibodies primarily by T-cell—independent mechanisms, and therefore, induce an immune system response that is neither long-lasting nor characterized by an anamnestic (i.e., booster)

* Corresponding author at: Respiratory Diseases Branch, CDC, 1600 Clifton Rd, Atlanta, GA 30333, United States. Tel.: +1 404 639 3585.
E-mail address: tpilishvili@cdc.gov (T. Pilishvili).

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response upon subsequent challenge with native polysaccharides. Therefore, antibody response to PPSV is poor in children aged <2 years whose immune systems are immature. In addition, polysaccharide vaccine does not reduce nasopharyngeal carriage of *S. pneumoniae* in children, and, therefore, is not associated with indirect (herd) effects.

PPSV23 has been recommended for adults ≥65 years old since 1983. Through 2012, a single dose of PPSV23 has been recommended for adults <65 years old with chronic medical conditions, as well as those with asthma or those who smoke cigarettes. A single revaccination with PPSV23 5 years after the initial dose was recommended before age 65 years for adults with immune compromise or those with functional or anatomic asplenia. In addition, a single dose of PPSV23 was recommended for all adults ≥65 of age regardless of previous history of PPSV23.

2.2. Pneumococcal conjugate vaccine—PCV13

The first pneumococcal conjugate vaccine, PCV7, was licensed in 2000 and recommended for use in infants and young children with a 4-dose schedule. Conjugate pneumococcal vaccine includes purified capsular polysaccharides of *S. pneumoniae*, each coupled with a nontoxic variant of diphtheria toxin, CRM197. Conjugation of polysaccharides to proteins changes the nature of the immune response to polysaccharide antigens from T-independent to T-dependent. This antigen complex stimulates a T-helper-cell response, leading to a substantial primary response among infants and a strong booster response at re-exposure.

Randomized clinical trials, as well as post-licensure observational studies have demonstrated that PCV7 prevents not only vaccine-type invasive pneumococcal disease but also pneumonia and acquisition of nasopharyngeal carriage of vaccine-type strains among children. This latter characteristic of PCV7 contributed to reduced transmission of vaccine-type strains to adults and, consequently, reductions in disease burden among adults (herd effects). The use of PCV7 among children has changed the epidemiology of pneumococcal disease in the United States. Although the vaccine was only recommended for children initially, its administration has resulted in dramatic declines in invasive pneumococcal disease in all age groups due to herd effects. As the serotypes in PCV7 declined, there was some replacement observed with increases in disease burden caused by non-vaccine serotypes [4]. In 2010, PCV13 replaced PCV7 for the vaccination of children. PCV13 contains the seven serotypes included in PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) and six additional serotypes (1, 3, 5, 6A, 7F, and 19A). By 2013, there were declines in invasive disease caused by the serotypes unique to PCV13 observed among all age groups similar to what was seen for PCV7 serotypes following PCV7 introduction [5]. The ability to demonstrate reduction in IPD due to several individual serotypes (1,3,5,6A) was limited because their incidence was too low or too inconsistent.

3. Recent changes in recommendations

In 2011, PCV13 was approved by the FDA for use among adults ≥50 years old to prevent pneumonia and invasive disease caused by the serotypes in the vaccine. It was approved under the FDA's accelerated approval pathway based on non-inferior immunogenicity compared to PPSV23. As a condition of licensure, the vaccine manufacturer agreed to conduct a randomized controlled trial of PCV13 against pneumococcal pneumonia in adults ≥65 years old [9]. The ACIP elected to recommend PCV13 for immunocompromised adults in 2012, but postponed making general recommendations in adults pending the results of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) [8] and additional data regarding the impact of PCV13 use in children on adult disease [5]. In 2014, after review of the results of CAPiTA and the impact of PCV13 indirect (herd) effects, ACIP recommended routine use of PCV13 in series with PPSV23 among adults ≥65 years [7]. In addition, in June 2015, ACIP revised the recommended intervals between PCV13 and PPSV23 for adults 65 years or older.

In adults ≥65 years of age who have not previously received a pneumococcal vaccine, the ACIP recommended the use of PCV13 followed by PPSV23 1 year or later. The ACIP further recommended that those who had previously received PPSV23 at age ≥65 receive PCV13 at least one year following the PPSV23 dose. Those who received PPSV23 before age 65 years who are now ≥65 years of age at the time of their visit should receive a dose of PCV13 at least one year after their last PPSV23, followed by a dose of PPSV23 at least a year after the PCV13 dose and at least 5 years following the previous PPSV23 dose. The recommendations for immunocompromised individuals passed by the ACIP in 2012 remained unchanged [10].

The ACIP further stated that recommendations for routine use of PCV13 among adults aged ≥65 will be reevaluated in 2018 and revised as needed. The recommendations for vaccine use are routinely reevaluated by the ACIP. There are already ample data to show that the herd effect of PCV13 vaccination in children will likely result in a diminished frequency of the vaccine serotypes in circulation and, therefore, diminished need for routine PCV13 vaccination among adults in the next few years.

4. Evidence supporting PCV13 use among adults

4.1. Immune response to PCV13

FDA approval of PCV13 in 2011 for adults was based on immunogenicity studies that compared antibody responses to PCV13 with antibody responses to PPSV23. In two randomized, multicenter, immunogenicity studies conducted in the United States and Europe, adults aged 50 years and older received a single dose of PCV13 or PPSV23. Functional antibody responses were measured 1 month after vaccination using an opsonophagocytic activity (OPA) assay. In adults aged 60 through 64 years naïve to pneumococcal vaccines, PCV13 elicited OPA geometric mean antibody titers (GMTs) to the 12 serotypes common to both vaccines that were comparable to, or higher than, responses elicited by PPSV23 [11]. For serotype 6A, which is unique to PCV13, OPA antibody responses were higher after PCV13 vaccination than after PPSV23 vaccination. OPA GMTs elicited by PCV13 in adults aged 50 through 59 years for all 13 serotypes were comparable to the corresponding GMTs elicited by administration of PCV13 in adults aged 60 through 64 years. In adults aged 70 years and older who previously had been immunized with a single dose of PPSV23 at least 5 years before enrollment, PCV13 elicited OPA responses that were comparable to or higher than those elicited by PPSV23 for the 13 serotypes. For 10 of 12 serotypes in common, the PCV13 responses were significantly greater than the PPSV23 responses [12]. At 1-year follow up, OPA levels were lower both in PCV13 and in PPSV23 recipients than at 1 month after immunization.

Four studies of PCV7 immunogenicity were conducted in the United States and Europe involving 699 HIV-infected subjects, all with CD4 counts of >200 cells/μl [13–16]. Response to a single dose of PCV7 was non-inferior or superior to PPSV23 for the serotypes evaluated. In an open label study among HIV-infected adults ≥18 years of age who previously received ≥1 doses of PPSV23, antibody response was measured following the receipt of 3 doses of PCV13 given 6 months apart [17]. The results of this study demonstrated that anticapsular polysaccharide immunoglobulin G concentrations and OPA titers were measured 1 month after each of the 3

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doses of PCV13, and, overall, antibody levels were similar after each dose. In addition, the number of prior PPSV23 doses received did not influence the immune response.

Overall, immunogenicity data suggest that PCV13 elicits a response as good or better (for some serotypes) than PPSV23 among adults, including those with HIV infection. However, the interpretation of these data are challenging without clinical efficacy studies because the level of vaccine-induced pneumococcal antibody in adults that correlates with protection against clinical disease, including IPD or pneumococcal pneumonia, has not been established.

4.2. Efficacy of PCV13 against invasive disease and pneumonia

A randomized placebo-controlled trial (CAPiTA trial) was conducted in the Netherlands among approximately 85,000 adults aged ≥65 years during 2008–2013 to verify and describe further the clinical benefit of PCV13 in the prevention of pneumococcal pneumonia [9]. The results of the CAPiTA trial demonstrated 45.6% (95% confidence interval [CI] = 21.8–62.5%) efficacy of PCV13 against all vaccine-type pneumococcal pneumonia, 45.0% (CI = 14.2–65.3%) efficacy against vaccine-type non-bacteremic pneumococcal pneumonia, and 75.0% (CI = 41.4–90.8%) efficacy against vaccine-type IPD among adults aged ≥65 years [8,18]. However, there was no impact on rates of all-cause community-acquired pneumonia or mortality, possibly due to the low proportion of community-acquired pneumonia attributable to vaccine type pneumococcus (13%) and the very small number of deaths in this population.

Efficacy of PCV7 against invasive pneumococcal disease (IPD) among immunocompromised adults was evaluated in a randomized control trial among 496 HIV-infected adults in Malawi [19]. The results of this trial demonstrated vaccine efficacy of 75% (95% CI 29–92%) in preventing IPD. In addition, the trial demonstrated the efficacy against all cause pneumonia of 25%, although not statistically significant. It is important to note that the study population differed from the general United States HIV-infected population in that all participants had survived a previous episode of IPD, only 13% were on anti-retrovirals, and the all-cause fatality rate was over 25%.

5. Evidence supporting PPSV23 use among adults

5.1. Efficacy of PPSV23 against IPD and pneumonia

While the results of studies evaluating PPSV23 efficacy and effectiveness against IPD are consistent with protection against IPD among generally healthy young adults and among the general population of older persons, studies of non-bacteremic pneumococcal pneumonia among adults have yielded contradictory conclusions. The meta-analysis by Moberley et al. [20] reported PPSV efficacy of 73% against vaccine type presumptive pneumococcal pneumonia. However, of the four studies contributing to this estimate [21–23], only one used the current formulation of PPSV23 [24] and it reported no efficacy against pneumonia (odds ratio of 1.04). Another meta-analysis conducted by Huss et al. showed no efficacy against pneumonia [25]. Two recent studies demonstrated efficacy of PPSV23 against non-bacteremic pneumococcal pneumonia [26,27]. A randomized trial by Maruyama et al. reported a 64% efficacy of PPSV23 against pneumococcal pneumonia among the residents of a long-term care facility. However, generalizability of the results of this study to the US population of adults ≥65 years old is limited. In addition, the efficacy was measured over a relatively short follow up period (26 months). There is a potential for misclassification of invasive pneumococcal cases as non-invasive pneumonia which would have led to an overestimate of vaccine efficacy against non-bacteremic pneumococcal pneumonia. The ratio of invasive to non-invasive pneumococcal pneumonia cases in this study was more than 5-times lower than expected (1:3) based on the recent meta-analysis of studies utilizing both urine antigen test and blood culture results [28]. A non-randomized 3-year observational study demonstrated 48% efficacy against non-bacteremic pneumonia on a smaller subset of study participants, after excluding PPSV23 vaccinations given >5 years prior to study enrollment [27]. However, interpretation of the results by Ochoa-Gondar, et al. is challenging given that the primary analysis utilizing the entire study cohort did not find effectiveness against non-bacteremic pneumonia.

Observational studies have demonstrated PPSV effectiveness ranging from approximately 50% to 80% for prevention of IPD among older adults and immunocompetent adults with various underlying illnesses [29]. A meta-analysis of PPSV23 based on pooled results of 10 RCTs suggested an overall efficacy of 74% against IPD [20].

6. Rationale and evidence for PCV13 and PPSV23 use in series

In 2013, of 13,500 cases of IPD estimated to have occurred among adults aged ≥65 years, approximately 20–25% of cases were caused by PCV13 serotypes and were potentially preventable with the use of PCV13 in this population (CDC unpublished data, 2013) [30]. An additional 38% of IPD among adults aged ≥65 years was caused by serotypes unique to PPSV23. Given this high proportion of IPD caused by serotypes unique to PPSV23, broader protection, especially against IPD, should be expected to be provided through use of both PCV13 and PPSV23 in series.

The evidence supporting the combined use of PCV13 and PPSV23 for adults is based on immunogenicity studies only. An evaluation of responses after a second pneumococcal vaccination administered one year after the initial study doses showed that a second dose of PCV13 generally resulted in OPA levels similar to those observed after the first dose. In contrast, subjects who received PPSV23 as the initial study dose had lower OPA antibody responses after subsequent administration of PCV13 than those who had received PCV13 as the initial dose, regardless of the level of the initial OPA response to PPSV23 [31]. Similar findings were observed in studies among HIV-infected adults; when PPSV23 and PCV were given in series, greater immune response was demonstrated when PCV was given first [14].

Several factors should be considered when determining the optimal interval between a dose of PCV13 and PPSV23, including immune response, safety, the risk window for protection against disease caused by serotypes unique to PPSV23, as well as practical considerations, such as timing for the next visit to the vaccination provider. None of the immunogenicity studies evaluating responses to PCV and PPSV23 administered in series was designed to evaluate the optimal interval between PCV and PPSV23. Studies evaluating the immune response after a sequence of PCV7 or PCV13 followed by PPSV23 with intervals of 2, 6, and 12 months or 3–4 years demonstrated that after the PPSV23 dose, antibody levels were higher than the pre-PCV baseline, and a non-inferior response was observed when compared with post-PCV antibody levels [31–34].

Although comparisons between various intervals could not be done within the same study, comparisons across several studies indicate that a longer interval between PCV13 administration and a dose of PPSV23 may be required to optimize the immune response to subsequent pneumococcal vaccine after an initial dose of conjugate vaccine [31–34]. However, extending the interval between PCV13 and PPSV23 should be carefully weighed against increasing

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the risk window during which the protection against IPD caused by serotypes unique to PPSV23 will not be provided.

Conversely, when minimizing the window between the two vaccines, safety data should be considered. One study directly compared 2 versus 6 month intervals between PCV13 and PPSV23 and showed that while the immune response was equivalent, increased reactogenicity was observed with a 2 month interval [32]. Lastly, practical aspects related to health-seeking behaviors of adults and expected timing of the next visit to a health-care provider should be considered to minimize missed opportunities. Recent national statistics indicate that nine out of ten adults 65 years of older have had at least one office visit to a doctor or other health professional in the past 12 months, and eight of ten adults in this age group had a medical encounter within the past 6 months [35].

7. Changing epidemiology and implications for use of pneumococcal vaccines among adults

Substantial reductions in the incidence of pneumococcal disease caused by serotypes in the 7-valent pneumococcal conjugate vaccine were noted among adults shortly after routine vaccination of children with PCV7 began in 2000 [36], and these reductions continued to occur through 2009 [4]. Recent studies demonstrate reductions in IPD caused by most serotypes in PCV13 across all age groups following only 3 years of PCV13 use among children (Fig. 1) [30]. Among adults of different age groups, reductions of 58–72% were observed by 2013. These findings demonstrate that PCV13 indirect effects observed to date are very similar to indirect effects of PCV7 during the same time period post-introduction. PCV13 serotypes currently account for approximately one fourth of IPD among adults aged 65 years and older (CDC, unpublished data, 2013). In addition, 11 serotypes that account for 38% of IPD in adults aged 65 years and older are included in PPSV23 but not in PCV13. In a setting of already observed PCV13 indirect effects, the new recommendation for routine PCV13 and PPSV23 use among adults 65 years or older is cost-effective and has the potential to prevent an additional 230 cases of IPD and approximately 12,000 cases of community acquired pneumonia, over the lifetime of a single cohort of persons aged 65 years, assuming 60% vaccination coverage among adults aged ≥65 years [7]. It is unclear whether the full impact of routine PCV13 vaccination among children on the incidence of adult IPD caused by PCV13 serotypes has already been observed or whether these reductions due to herd effects will continue to occur among adults. Recently conducted analysis demonstrated that potential impact of PCV13 use among adults can be maximized with rapid uptake and improved vaccine coverage during the first 3 years post-PCV13 introduction among adults, and the largest impact is expected in the short-term [37]. In the long-term, if indirect effects of PCV13 use among children continue to reduce the burden of vaccine type disease among adults, the benefit of vaccinating adults with PCV13 is likely to be reduced substantially. This consideration led to ACIP decision to recommend that the new recommendations for PCV13 and PPSV23 use among adults ≥65 years old be re-evaluated and revised, if needed, in 2018.

Before ACIP revisits this recommendation, the impact of PCV13 use in the target population of adults ≥65 years old should be monitored. Vaccine uptake for both PCV13 and PPSV23 should carefully be monitored through existing systems [38,39], as well as through state immunization registries, where available. Coverage for PPSV23 remains well below Healthy People 2020 targets among adults ≥65 years of age, and in spite of the routine recommendations available since 1983, modest increases in coverage were observed only in recent years [1,38]. Given that the full PCV13 indirect effects through the vaccine use in children may not have been observed, and vaccine-preventable disease burden remains among adults, rapid uptake of PCV13 among adults can maximize the benefits of the new ACIP recommendation. Since the experience with PCV7 has demonstrated the marked reduction, almost disappearance, of PCV7 serotypes, the ACIP anticipates that PCV13 childhood vaccination alone may eliminate the additional serotypes rendering adult vaccination of limited value in the future. However considering the current residual disease among adults, PCV13 immunization in the short-term may prevent substantial pneumococcal disease.

Laboratory-based surveillance systems monitoring pneumococcal infections are best positioned to track the impact of the pediatric PCV13 program on invasive disease burden among adults [40]. In addition, studies evaluating the post-licensure effectiveness of PCV13 among adults ≥65 years old are needed. These will likely include vaccine effectiveness studies addressing IPD and non-bacteremic pneumococcal pneumonia using a case control design, and studies of the impact of vaccine on carriage among adults. The burden of pneumococcal disease in adults is mainly determined by CAP, and while microbiological diagnosis to establish etiology of CAP underestimates the burden of pneumococcal

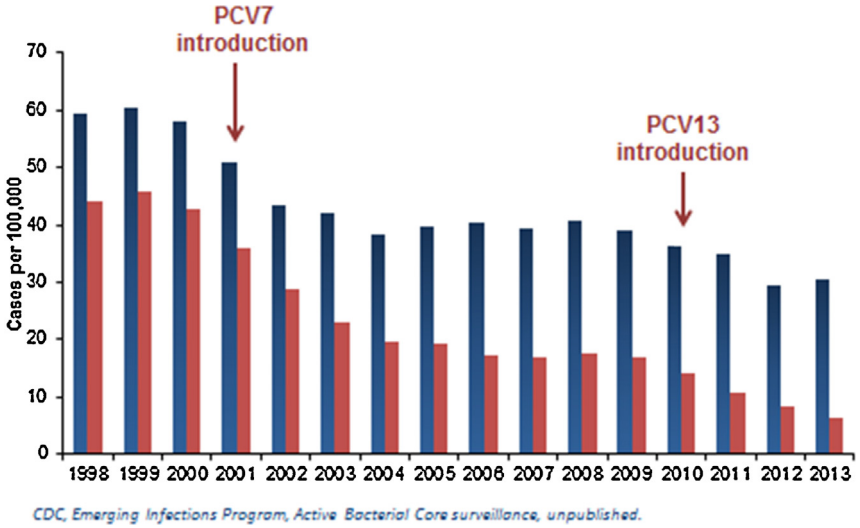

Fig. 1. Changes in the incidence of invasive pneumococcal disease among adults ≥65 years old, 1998–2013. Blue bars = IPD caused by all serotypes; red bars = IPD caused by PCV13 serotypes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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pneumonia, studies utilizing non-culture based urine antigen tests can help monitor changes in overall burden of pneumococcal CAP [41]. A recently developed serotype-specific urine antigen test was used in the CAPiTA trial to diagnose PCV13-type non-bacteremic pneumococcal pneumonia [8] and has also been applied in studies to determine the burden of PCV13-type CAP among adults [42,43]. However, before similar tests can be broadly used to monitor changes in serotypes causing non-bacteremic CAP, they should be developed for a broader research use and wider range of pneumococcal serotypes. When the ACIP reviews the value of PCV13 vaccination among adults in 2018, the results of these studies will assist in distinguishing the effects of herd immunity from the direct impact of adult vaccination. Specific criteria for changing the current recommendation have not been determined but will be based on these studies.

In addition to the studies of the impact of PCV13 via direct and indirect effects on adult disease burden, there are critical areas for further research. Little is known regarding the duration of protection for conjugate vaccines among adults and the need for revaccination. If ACIP re-evaluation in 2018 suggests that PCV13 should continue to be used for adults, duration of protection and need for revaccination would become a concern. Efficacy of a single dose of PCV13 was evaluated in the CAPiTA trial, and for the duration of the study follow up (3–4 years) no waning of efficacy was observed [8]. However, no further systematic follow-up of the CAPiTA trial is planned to assess duration of protection. While immunogenicity studies evaluating revaccination with PCV13 suggest that a response to repeat doses is non-inferior to the one observed following the initial dose, the clinical relevance of this finding in the absence of correlates of protection for adults is unknown [31,34]. In addition, the optimal intervals for revaccination to maintain population protection are unknown. The benefits of conjugate versus polysaccharide vaccines, although apparent in the short run, will require further study and observation as the epidemiology of specific pneumococcal serotypes evolves.

The new recommendations for PCV13 use among adults ≥65 years old along with the pediatric PCV13 use will continue to apply pressure on vaccine-type disease among adults. The declining burden of PCV13-type disease and colonization among unvaccinated populations of adults due to the indirect effect of vaccinating children may signal that routine PCV13 use among adults will have limited utility, and the continued benefits may be maintained through pediatric use of the vaccine. Revised cost effectiveness evaluations incorporating changes in disease burden observed through PCV13 direct and indirect effects, uptake of the vaccine in the target population, and the cost of the vaccines will help align this recommendation for PCV13 use with other adult vaccines in use. Monitoring changes in the distribution of serotypes causing pneumococcal disease among children and adults should inform formulations of future higher-valent conjugate vaccines. Formulations for adult conjugate vaccines different from the one licensed for children should also be explored to complement the indirect effects from PCV13 use in children. Continued efforts in the development of common protein-based or inactivated whole cell vaccines hold the promise to confer broader serotype-independent protection against pneumococcal disease.

8. Summary

The ACIP has recently made recommendations for the use of pneumococcal vaccines in healthy adults >65 years. These recommendations for both PCV13 and PPSV23 were based on the remaining burden of illness among adults caused by PCV13 serotypes and by those serotypes included in PPSV23 and not PCV13. The committee also considered the importance of non-bacteremic pneumococcal pneumonia in determining the overall burden of pneumococcal disease among adults and the evidence from CAPiTA confirming the efficacy of PCV13 to prevent pneumonia among older adults. The optimal order of vaccination and intervals between PCV13 and PPSV23 recommendations were based on the best available evidence and on practical considerations. Close scrutiny of the changing epidemiology of IPD and pneumonia will be required to evaluate the effectiveness and the continued utility of the current vaccination strategy, and the future directions for pneumococcal disease prevention among older adults.

Conflict of Interest

None declared.

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